REMARKS/ARGUMENTS

Applicant responds to the Examiner's comments using the paragraph numbering of the office action. Support for variants associated with hereditary amyloidosis as recited in amended claim 11 is provided by *e.g.*, Table 2 at p. 17. Support for the recital that the immune response to an amyloid component includes antibodies in amended claim 11 is provided at *e.g.*, p. 13, lines 10-25. Support for an adjuvant that augments an immune response is provided at *e.g.*, p. 11, lines 10-15. Unless otherwise indicated amendments are for purposes of clarity. No amendment should be viewed as an acquiescence in any ground of rejection.

1. Traverse of the restriction requirement is maintained for the reasons previously indicated, and will be taken up on petition.

4. Information disclosure statements.

Applicant's citation of the references has included all the elements required to comply with 37 C.F.R. §§ 1.97-98 that are known to them.

5. The specification.

The specification was objected to as having informalities. Applicant has amended the specification to correct informalities and requests that the objection be withdrawn.

The cross reference to related application section has been replaced with a replacement section which provides domestic priority information for the instant case. A supplemental ADS providing domestic priority information is submitted herewith to satisfy the specific reference requirement of 35 U.S.C. § 119(e) and § 120.

The addition of page 96, which was inadvertently omitted from the instant application as filed, to the specification does not add new matter. The instant application incorporates U.S. Application No. 60/137,010 by reference (*see* p. 2, lines 5-6 of the instant application). Support for the addition of page 96 is provided at page 87, line 29 to page 88, line

20 of U.S. Application No. 60/137,010. For the convenience of the Examiner, applicant has attached pages 87 and 89 of U.S. Application No. 60/137,010 as Exhibit A.

As requested by the Examiner, the brief description of the drawings section of the specification has been amended to recite a brief description of Figs. 15A, 15B, 15C, 15D, and 15E.

The specification has also been amended to conform to five of the replacement drawing sheets submitted herewith, *i.e.*, Fig. 15A, Fig. 15B, Fig. 15C, Fig. 15D, and Fig. 15E, respectively. The paragraph beginning on page 10, line 26, has been replaced with six replacement paragraphs. The replacement paragraphs describe Figures 15A-15E, 15A, 15B, 15C, 15D, and 15E, respectively. The paragraph beginning on page 94, line 1, has also been amended to identify Figures 15A-15E.

The paragraphs beginning on page 91, line 17, and page 92, line 3, have been amended to conform the alum concentration to the alum concentration recited in Figure 15 as filed in Application No. 09/201,430, filed November 30, 1998. The instant application claims priority to Application No. 09/201,430.

6. Sequence rules.

The office action mailed November 21, 2002 enclosed a notice to comply with the sequence listing rules. On May 15, 2003, applicant brought the instant application into compliance with the sequence rules by submitting the following papers to the Office, via Express Mail Post Office to Addressee, in an envelope addressed to Mail Stop Sequence, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450: a paper copy of the Sequence Listing, an electronic copy of the Sequence Listing, and an Amendment under 37 C.F.R. §§ 1.821-1.825.

7. Drawings.

Amendments to Figure 11

As requested by the Examiner, Figure 11 has been amended to add a legend. Support for this amendment can be found at page 77, line 17 to page 78, line 29 of the specification.

Amendments to Figures 15A-15E

As requested by the Examiner, the brief description of the drawings section of the specification has been amended to recite a brief description of Figs. 15A, 15B, 15C, 15D, and 15E.

Figures 15A-15E have been amended to correct an obvious error, *i.e.*, "p Malue" has been replaced with "p Value." Figure 15D as filed in the instant application discloses an alum concentration of 2μg/ml. Amended Figure 15D discloses an alum concentration of 2 mg/ml. Support for both of these amendments is provided by the informal Figure 15 as originally filed in the parent application. Thus, the amendments to the Figs. 15A-E contain no new matter.

Amendments to Figure 16

The descriptive term "Anti AB" has been replaced with the term "Anti-Abeta" to give greater clarity to the title. Support for this amendment can be found on page 92, lines 25-33 of the specification.

8. The Examiner objects to the claims 11-25 as containing nonelected material. Because the additional restriction requirement has been traversed and may be modified as a result of a petition, it would be premature to delete nonelected material from the claims. However, applicant agrees to do so, if the additional restriction requirement is upheld on petition.

If the additional restrict requirement is not modified as a result of a petition, it is applicant's position that only claims 13 and 15 contain nonelected material. Applicant elected

Group II, claims 11-25. Applicant was also required to make an election in response to the additional restriction requirement.

> "Upon election of one of Groups I-VI, Applicant is additionally required to elect a single amyloid component, agent and fibril components from each of claims 3, 5-6, 13, 15, 34-35 and 49-50, (depending on the inventive Group, which is elected)."

See paragraph 10 of the restriction requirement mailed March 27, 2002.

Applicant elected claims 13 and 15 with traverse. Applicant respectfully points out that claims 11-12 and 16-25 were not to subject to the additional restriction requirement. Thus, claims 11-12 and 16-25 cannot contain nonelected material.

9-19. Rejections under 35 U.S.C. § 112, first paragraph. Due to the length of this rejection applicant will address each paragraph in turn starting with paragraph 10.

10. The Examiner merely summarizes the claims. No response is required.

11. The Examiner alleges that the PDAPP mouse model does not exhibit Alzheimer's disease, Down's syndrome or other amyloidogenic disease as evidenced by Schenk and Games. Insofar as the Examiner is suggesting that the PDAPP mouse model is not a good model of Alzheimer's disease or Down's syndrome in humans, Applicant disagrees. The PDAPP mouse used in the present examples has been recognized in the art as being a major breakthrough in the production of an animal model for Alzheimer's disease. The importance and breakthrough nature of the PDAPP mouse is indicated by the fact it was the cover story in that edition of Nature in which it was first described (Games et al., *Nature*, 373(6514): 523-527 (1995)). PDAPP transgenic mice described in Games exhibit age- and brain region-dependent development of typical amyloid plaques, dystrophic neurites, loss of presynaptic terminals, astrocytosis and microgliosis. These lesions in the PDAPP mouse brain tissue typify many of the neuropathological hallmarks associated with Alzheimer's disease. Games also describe

neurodegeneration and inflammation characteristic of Alzheimer's disease, with associated Aβ plaque deposition and certain regions of afflicted brain parenchyma, are present in the mice genetically engineered with the construct. Deposition of brain deposits increases with age, as in the case of Alzheimer's disease. Thus, the PDAPP mouse does model much of the pathology seen in Alzheimer's disease patients.

The Schenk and Games references contradict rather than support the Examiner's allegations of inadequacy of the PDAPP mouse model. As noted above, Games appeared as the cover story of Nature and describes many characteristics of the PDAPP mouse that closely resemble the pathology in Alzheimer's disease. The reference concludes:

> A most notable feature of these transgenic mice is their Alzheimer-like neuropathology.... Our transgenic model... offers a means to test whether compounds that lower Aβ production and/or reduce its neurotoxicity in vitro can produce beneficial effects in an animal model prior to advancing such drugs into human clinical trials.
>
> p. 527, first column, second paragraph.

Similarly, Schenk, which also formed the cover story of the edition of Nature (*see* Schenk et al., *Nature*, 400:173-177 (1999)) in which it appeared, concludes

> Collectively, the results suggest that amyloid-β immunization may prove beneficial for both the treatment and prevention of Alzheimer's disease.
>
> p. 177 paragraph bridging cols. 1 and 2.

The validity of the PDAPP mouse as a model system for predicting effects of Aβ in humans is further confirmed by the results of human clinical trials. (As previously noted, the Examiner's comments regarding side effects observed in these trials will be addressed separately below.) The Investigational New Drug Application ("INDA") supporting the clinical trials was based on essentially the same data as is contained in the present application. That the FDA allowed clinical trials to occur shows that it considered the preclinical evidence, including the results in PDAPP mouse, as being reasonably predictive of success in humans.

12. The Examiner alleges that administration of Aβ42 to Alzheimer's patients is not predictive of how administration of transthyretin or ATTR affects diseases caused by these proteins. Initially, it is noted that the claims do not specifically recite that transthyretin is administered but rather that an amyloid component derived from transthyretin (*e.g.*, ATTR) is administered. With respect to the Examiner's position that administration of Aβ42 is not predictive of other amyloid peptide based diseases, applicant notes evidence showing analogous results for two other amyloid peptides, namely, synuclein and prion protein (PrP). The specification describes an example in which antibodies to various epitopes of Aβ and antibodies to synuclein were tested in an *ex vivo* assay for capacity to clear amyloid deposits from brain tissue in the presence of phagocytic cells (*see* pp. 113-117). The antibodies to Aβ were also tested in the PDAPP mouse model. The results from the *ex vivo* model show excellent correlation with those *in vivo*: antibody to Aβ that cleared deposits *ex vivo* also cleared deposits *in vivo*. Because antibodies to synuclein were found to clear amyloid deposits characteristic of Alzheimer's disease *ex vivo* and because of the excellent correlation between *ex vivo* and *in vivo* results, one would reasonable expect that antibodies to synuclein would also clear amyloid deposits *in vivo*. Thus, administration of synuclein with an adjuvant is reasonable expected to clear amyloid deposits in similar fashion to Aβ. Likewise, closely analogous results have been reported for administration of PrP or antibodies thereto. Applicant attaches two publications dated after the priority date of the present invention showing that active immunization with PrP and passive administration of antibodies to PrP in a mouse model of prion disorder diseases produces results similar to those described for immunization of Aβ (*see* Sigurdsson *et al.*, *Am. J. Pathol.* 161, 13-17 (2002) (active); Sigurdsson *et al.*, *Neuroscience Letters* 336, 185-187 (2003) (passive), attached hereto as Exhibits C and D, respectively).

Although the precursor proteins in different amyloid diseases do not share sequence homology or related native structure, the morphology and properties of all amyloid fibrils are remarkably similar (*see* Sunde *et al., J. Mol. Biol.*, 1997 Oct 31;273(3):729-739). All give similar high-resolution X-ray fiber diffraction patterns, consistent with a helical array of beta-sheets parallel to the fiber long axis, with the strands perpendicular to this axis irrespective of the nature of their precursor proteins (*Ibid*). Given the common structure of amyloid deposits

in different diseases, the likelihood that immunization of any amyloid peptide with an adjuvant in an appropriate regime will generate antibodies, and the demonstration that antibodies to three different amyloid peptides (Aβ, synuclein, and PrP) have clearing activity against amyloid deposits, it is likely that what has been observed for Aβ in treatment of Alzheimer's disease is generally true for other amyloid peptides in treatment of other amyloidogenic diseases.

13. The Examiner cites several papers (Lemere, Schenk, DeMattos and Raso) as evidence that therapy can be effective in removal of amyloid plaques. The Examiner does not indicate how any of this evidence detracts from enablement of the present claims. Accordingly, it is believed no response is needed.

14. The Examiner says one would doubt the claimed method would work due to lack of information as to specific biological actions/activities that a ATTR protein and an adjuvant would effect, lack of information how the immunogenic effect on amyloid deposition relates to symptoms of disease, and an alleged expectation ATTR would be actively involved in amyloid deposition (citing Kline, US 5,851,996; Potter, US 5,780,587; and, Perutz, *PNAS*, 99(8):5591-5595 (2002)). These points will be addressed in turn. The result that passive administration of Aβ or PrP achieves essentially the same results as active administration of Aβ or PrP shows that active administration of amyloid peptides acts, at least in part, through formation of antibodies. With respect to how the immunogenic effect of amyloid peptide administration relates to symptoms of disease, one would expect similar symptomatic effects results from other amyloid peptides as Aβ in view of the similarity in the structure of the amyloid deposits that form the hallmark pathologies in the diseases.

The Kline, Potter, and Perutz references provide no reason to think that exogenously supplied Aβ, particularly in combination with an adjuvant, adds to existing plaques rather than clearing plaques as demonstrated in the present examples. Kline discusses treatment with very low dosages of Aβ. Potter discusses screening for compounds that inhibit binding of Aβ to apolipoprotein E4 of alpha-1 antichymotrypsin. These compounds include certain fragments of Aβ. Perutz discusses crystallographic analysis of the structure of amyloid fibers.

Thus, none of these references contradicts the evidence in the present application that administration of Aβ with an adjuvant clears Aβ deposits rather than adding to them.

It is not apparent how the Stein and Tennent references cited by the Examiner are relevant to the above issues. Stein discusses expression of several genes in the brains of transgenic mice that may be induced in response to accumulation of Aβ. Tennent discusses a role of serum amyloid P protein in rendering amyloid plaques resistant to degradation. Neither reference appears detrimental to enablement.

15. The Examiner alleges that undue experimentation would be required to evaluate all possible aspects of both humoral and cellular aspects of the immune response. The Examiner cites Chapman, Frenkel (1999), Frenkel (1998), Frenkel (2000), and Freidland (1997) as alleged evidence of the unpredictable effects of antigens on the immune system. In response, an understanding of mechanism is not required to practice the claim as presently formulated. The claims as presently formulated specify that one administers a dosage of synuclein or a fragment thereof effective to induce antibodies to an amyloid component derived from synuclein in combination with an adjuvant that augments the immune response. The result of treating or preventing a synuclein based disease follows from performing the claims as written without the need to understand how the induced antibodies effect this result.

It is not seen that the cited references are detrimental to enablement. Friedland discusses possible use of labeled Aβ as agent for imaging plaques in the brain. However, the Aβ is not proposed to be administered with an adjuvant or otherwise to generate an immune response comprising antibodies. Thus, there is nothing in Frenkel to suggest that the combination of Aβ and an adjuvant would not be effective in preventing or treating Alzheimer's disease. The various Frenkel references investigate the role of an N-terminal epitope of Aβ, and propose to display it from a phage for use as an immunogen to generate antibodies in a mouse model of Alzheimer's disease. This proposal appears closely related to one embodiment disclosed in the present application (which predates the Frenkel references) (*see* specification at p. 11, lines 10-14). That others have incorporated the teaching of the present application into their own work supports rather than refutes enablement of the present claims. Finally, Chapman

reviews three papers that test antibodies to Aβ for effects of potential treatments of both brain damage and cognitive losses caused by Alzheimer's disease. Chapman concludes that "All in all, though, these three papers give cause for optimism" (at p. 916, first column, last paragraph). Thus, again Chapman supports rather than contradicts enablement of the present claims.

16. The Examiner alleges undue experimentation would also result from inflammatory side effects (citing to Elan press releases, Grubeck-Loebenstein, and US 5,958,883). It is respectfully submitted that requiring a patent applicant to teach means for avoiding all side effects imposes too high a standard of enablement. Here, clinical trials have indicated that inflammatory side effects may result in a small number of patients (15 out of 360), as discussed in the Elan press releases, and Munch (made of record as cite no. 359). Moreover, in the few patients that might experience side effects, there is the possibility of mitigation by immunsuppressants (*see* Munch at p. 1085). Few approved drugs, particularly those for treating serious diseases, are entirely free of side effects. Moreover, the requirements under the law for obtaining a patent are not as stringent as the requirements for obtaining government approval to market a particular drug for human consumption. *In re Brana*, 34 USPQ2d 1436, 1442 (Fed. Cir. 1995). "Testing for full safety and effectiveness...is more properly left to the Food and Drug Administration (FDA). Title 35 does not demand that such human testing occur within the confines of Patent and Trademark Office (PTO) proceedings." *Ibid.*

17. The Examiner alleges additional unpredictability due to the recital of mutant proteins, peptides and fragments. The language referred to by the Examiner appears in claim 13 in reference to the description of precursor proteins. The references to peptides and fragments have been deleted from amended claim 13 as not further limiting the precursor proteins referred to in the claims. The reference in claim 13 to mutant proteins has also been amended to specify variants associated with hereditary amyloidosis. These are not random mutations, which may have the unpredictable effects, but rather natural mutations known to associated with amyloidogenic disease. There is no reason to think that immune responses directed to amyloid components derived from precursor proteins having such mutations would be less effective in

treating ATTR protein disorders than immune responses directed to components from a wildtype precursor protein.

18. The Examiner cites Tanaka as evidence that administration of Aβ to the cerebral ventricle of rats produces learning and memory deficits accompanied by dysfunction in the cholingeric and dopaminergic systems. In response, it is noted that Tanaka administered Aβ without an adjuvant thereby placing it outside the claims. Further, it is noted that the combination of conditions used by Tanaka was specifically chosen with a view to aggregating Aβ in the brain as a model of Alzheimer's disease rather than clearing such deposits. Thus, Tanaka administered Aβ directed to the brain, by continuous infusion, and without an adjuvant. A skilled person intending to generate an immune response comprising antibodies with a view to clearing Aβ deposits could easily avoid such a combination of conditions calculated to achieve the opposite effect.

19. The Examiner alleges that the application must establish a nexus between the specific immune response recited in the claims for each amyloid disorder and the alleviation of the disease state. The Examiner alleges that the skilled artisan is not guided as to how an immune response must effectuate one or more actuates of each targeted protein such that the immune response would alleviate the disorder. The Examiner also refers to variation between different amyloid disorders (citing Small, Chapman, Esiri, St. George-Hyslop, Younkin, Tennent, and Stein).

As previously discussed, the application does provide evidence that an antibody component of an immune response to peptide administration is, at least in part, responsible for alleviation of the disease state. This is shown by the result that passive immunization with antibodies achieves essentially the same results as active immunization with peptides (both with Aβ and prion protein). Further understanding of mechanisms by which antibodies lead to clearing of amyloid deposits is not required for practice of the invention. Nevertheless, the application does provide data showing that induction of a phagocytitic clearing response is involved, at least in part, in the clearing response due to antibodies to Aβ.

The Examiner's additional comments regarding possible variation between different types of amyloid disease have discussed above. To reiterate, all amyloid deposits have a common structure, all amyloid peptides are expected to generate antibodies in an appropriate regime with an adjuvant, and in each of three amyloid components tested (Aβ, synuclein, and prion protein). Therefore, there is an expectation that the same strategy and principles of immunizing with an amyloid peptide and an adjuvant to generate an antibody response is a general approach for treating amyloidogenic diseases.

20. The claims are provisionally rejected for same invention double patenting over claims of several copending cases. Applicant requests this issue be held in abeyance until indication of otherwise allowable subject matter. It is likely in view of the restriction and election of species requirements that the claims in the cited cases will differ from those pending in the current case at the time of allowance of the present case. However, if claims from different cases are in conflict at that time, applicant will amend the claims in the cited cases to avoid the conflict.

21-28. The claims stand provisionally rejected for obviousness type double patenting over several copending cases. Applicant proposes the issues be held in abeyance until indication of allowability in the present case. Applicant will then consider providing a terminal disclaimer over cited cases provided the cited case has been or is about to patented, the claims in the cited case have not been divided from those in the present case by restriction requirement or election of species, and the claims in the cited case are in conflict with those in the present case at this time.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,

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